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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/743,163	12/22/2003	Mehmet Inan	15948Z	7785

23389 7590 09/19/2007

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ART UNIT	**PAPER NUMBER**
1636	

MAIL DATE	DELIVERY MODE
09/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/743,163	INAN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23 and 31-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *23,36-38,40,42,44,46,48,50,52 and 54* is/are allowed.

6)☒ Claim(s) *31-35, 39,41,43,45,47,49,51,53 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 6/18/2007, in which claims 1-22 and 24-30 were canceled, and claims 31-55 were newly added. Currently, claims 23 and 31-55 are pending and under consideration.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Response to Arguments - Double Patenting

Applicant's arguments, see page 7, filed 6/18/2007, with respect to the rejection of claims 5 and 7-22, as being unpatentable over claims 1 and 5-20 of U.S. Patent No. 6,699,691, have been fully considered and are persuasive. The previous rejection of claims 5 and 7-22 has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43, 45, 47, 49, 51, 53 and 55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection, necessitated by the addition of new claims 43, 45, 47, 49, 51, 53 and 55 in the reply filed 6/18/2007.

Claim 43 recites the limitation "said host cell" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend claim 41 to recite a "host cell" rather than merely "host."

Claims 45, 47 and 49 depend from claim 43 and are thus indefinite for the same reason applied to claim 43.

Claim 51 recites the limitation "the host cell" in line 1. There is insufficient antecedent basis for this limitation in the claim. It would be remedial to amend claim 41 to recite a "host cell" rather than merely "host."

Claims 53 and 55 depend from claim 51 and thus are indefinite for the same reasons applied to claim 51.

Response to Arguments - 35 USC § 112

The rejection of claims 1-22 under 35 U.S.C. 112, second paragraph is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

The rejection of claims 26-30 under 35 U.S.C. 112, first paragraph (new matter) is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

The rejection of claims 1-22 under 35 U.S.C. 112, first paragraph (written description) is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 39, 41, 43, 45, 47, 49, 51, 53 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Sears et al (Yeast, Vol. 14, pages 783-790, 1998, cited in a prior action; see the entire reference), as evidenced by GenBank Accession No. AF027961 (Publicly available 7/1/1998, cited in a prior action). This is a new rejection, necessitated by the addition of new claims 39, 41, 43, 45, 47, 49, 51, 53 and 55 in the reply filed 6/18/2007.

The claims are drawn to or encompass a recombinant vector comprising a 5' regulatory sequence operably linked to a heterologous coding region, wherein said 5' regulatory region consists of an isolated polynucleotide according to any of claims 31-35. Claims 31-35 are drawn to isolated polynucleotides consisting of SEQ ID NO: 16-19 and 21, respectively. The use of "consists" in the body of the claim does not limit the open-ended "comprising" language in the claim. Thus, the claims encompass vectors with additional regulatory sequences present, as long as the vector contains the specific sequence recited by any one of claims 31-35. See MPEP § 2111.03.

Sears et al teach expression plasmid pIB4, an isolated, double-stranded polynucleotide comprising an AOX1 promoter that contains a fragment of instant SEQ ID NO: 17, the entire sequence of instant SEQ ID NO: 18, the entire sequence of SEQ ID NO: 19, the entire sequence of SEQ ID NO: 20, and a fragment of SEQ ID NO: 21, and complements thereof (e.g. page 785, left column, 3rd full paragraph; Figure 1). GenBank Accession No. AF027961 is cited only to show that the nucleotide sequence of plasmid pIB4 contains the abovementioned sequences. See the alignments in Exhibits I-V (mailed 12/14/2006). Sears et al teach plasmid pIB4-GUS, in

which the GUS coding sequence was placed under the control of the AOX1 promoter (e.g. page 785, left column, last paragraph). The pIB4-GUS plasmid contains, in 5' to 3' order, the abovementioned AOX1 promoter, the heterologous GUS coding region, and an AOX1 terminator sequence (e.g. page 785, left column, last paragraph; page 786, right column, last paragraph). Sears et al teach *Pichia pastoris* host cells comprising vector pIB4-GUS (e.g. page 786; page 788, second full paragraph). The GUS protein was expressed in the transformed yeast cells and partially isolated for enzyme assays (e.g. page 786; Table 2).

Claims 39, 41, 43, 45, 47, 49, 51, 53 and 55 are rejected under 35 U.S.C. 102(b) as being anticipated by Stroman et al (U.S. Patent No. 4,855,231, cited as reference 3 on the IDS filed 12/22/2003; see the entire reference), as evidenced by GenBank Accession No. I02097 (publicly available 5/21/1993). This is a new rejection, necessitated by the addition of new claims 39, 41, 43, 45, 47, 49, 51, 53 and 55 in the reply filed 6/18/2007.

The claims are drawn to or encompass a recombinant vector comprising a 5' regulatory sequence operably linked to a heterologous coding region, wherein said 5' regulatory region consists of an isolated polynucleotide according to any of claims 31-35. Claims 31-35 are drawn to isolated polynucleotides consisting of SEQ ID NO: 16-19 and 21, respectively. The use of "consists" in the body of the claim does not limit the open-ended "comprising" language in the claim. Thus, the claims encompass vectors with additional regulatory sequences present, as long as the vector contains the specific sequence recited by any one of claims 31-35. See MPEP § 2111.03.

Stroman et al teach an isolated DNA fragment comprising a regulatory region containing a nucleotide sequence which is 100% identical to instant SEQ ID NOS: 17, 18, 19 and 21. See claims 3 and 19 of Stroman et al. GenBank I02097 is cited only to show that the nucleotide sequences disclosed in Stroman et al contain the abovementioned sequences. See the sequence comparisons in Exhibits VI-XII (mailed 12/14/2006). Moreover, Stroman et al teach plasmid pSAOH5, which contains instant SEQ ID NOS: 16-21 (e.g. Example XIV). This is the same plasmid used in the instant specification, and thus it would necessarily have the same sequence as the instant sequence identifiers. Stroman et al teach a recombinant vector comprising the DNA fragment (see the claims and the figures), an expression cassette comprising the DNA fragment operatively linked to a heterologous coding region (such as the lacZ gene), and a termination sequence is taught (see the figures and claim 33, for example). A *Pichia pastoris* cell comprising the vector or expression cassette is taught (columns 67-68, for example). A method for the production of protein is taught comprising growing cells transformed with the vector or expression cassette so that the protein is expressed and isolating the expressed protein (column 67, for example).

Claims 39, 41, 43, 45, 47 and 49 are rejected under 35 U.S.C. 102(b) as being anticipated by Buckholz (EP 0244598, cited in a prior action; see the entire reference). This is a new rejection, necessitated by the addition of new claims 39, 41, 43, 45, 47 and 49 in the reply filed 6/18/2007.

The claims are drawn to or encompass a recombinant vector comprising a 5' regulatory sequence operably linked to a heterologous coding region, wherein said 5' regulatory region

consists of an isolated polynucleotide according to any of claims 31-35. Claims 31-35 are drawn to isolated polynucleotides consisting of SEQ ID NO: 16-19 and 21, respectively. The use of "consists" in the body of the claim does not limit the open-ended "comprising" language in the claim. Thus, the claims encompass vectors with additional regulatory sequences present, as long as the vector contains the specific sequence recited by any one of claims 31-35. See MPEP § 2111.03.

Buckholz teaches an isolated DNA fragment comprising a regulatory region containing instant SEQ ID NOS: 16, 17, 18, 19, 20 and 21. See claims 1-3 and plasmid pSAOH5 in Figure 2. Plasmid pSAOH5 is the same plasmid used in the instant specification to isolate the AOX1 promoter sequences, and thus it would necessarily have the same sequence as the instant sequence identifiers. Buckholz teaches a recombinant vector comprising the DNA fragment (see page 4). An expression cassette comprising the DNA fragment operatively linked to a heterologous coding region (such as the lacZ gene) and a termination sequence is taught (see claims 4-5 and page 4). A *Pichia pastoris* cell comprising the vector or expression cassette is taught (page 4).

Response to Arguments - 35 USC § 102

The rejection of claims 1-22 under 35 U.S.C. 102(b) as being anticipated by Sears et al, as evidenced by GenBank Accession No. AF027961, is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

The rejection of claims 1-22 and 24 under 35 U.S.C. 102(b) as being anticipated by Stroman et al, as evidenced by GenBank Accession No. I02097, is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

The rejection of claims 1-20, 24 and 25 under 35 U.S.C. 102(b) as being anticipated by Buckholz is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

With respect to the new rejections set forth above, Applicant's arguments filed 6/18/2007 have been fully considered but they are not persuasive. The response asserts that the references do not teach a polynucleotide consisting of SEQ ID NO: 16, 17, 18, 19 or 21, as recited in claims 31-35. While the references do not teach the sequences consisting of SEQ ID NO: 16, 17, 18, 19 or 21, the references do teach vectors containing a regulatory region containing the sequence of at least one of SEQ ID NO: 16, 17, 18, 19 or 21. The rejected claims are drawn to or encompass a recombinant vector comprising a 5' regulatory sequence operably linked to a heterologous coding region, wherein said 5' regulatory region consists of an isolated polynucleotide according to any of claims 31-35. Claims 31-35 are drawn to isolated polynucleotides consisting of SEQ ID NO: 16-19 and 21, respectively. The use of "consists" in the body of the claim does not limit the open-ended "comprising" language in the claim. Thus, the claims encompass vectors with additional regulatory sequences present, as long as the vector contains the specific sequence recited by any one of claims 31-35. See MPEP § 2111.03.

> When the phrase "consists of" appears in a clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole. *Mannesmann Demag Corp.* v. *Engineered Metal Products Co.*, 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986). >See also *In re Crish*, 393 F.3d 1253, 73 USPQ2d 1364 (Fed. Cir. 2004) (The claims at issue "related to purified DNA molecules having promoter activity for the human involucrin gene (hINV)." *Id.*, 73 USPQ2d at 1365. In determining the scope of applicant's claims directed to "a purified oligonucleotide comprising at least

> a portion of the nucleotide sequence of SEQ ID NO:1 wherein said portion consists of the nucleotide sequence from ... to 2473 of SEQ ID NO:1, and wherein said portion of the nucleotide sequence of SEQ ID NO:1 has promoter activity," the court stated that the use of "consists" in the body of the claims did not limit the open-ended "comprising" language in the claims (emphases added). *Id.* at 1257, 73 USPQ2d at 1367. The court held that the claimed promoter sequence designated as SEQ ID NO:1 was obtained by sequencing the same prior art plasmid and was therefore anticipated by the prior art plasmid which necessarily possessed the same DNA sequence as the claimed oligonucleotides. *Id.* at 1256 and 1259, 73 USPQ2d at 1366 and 1369.The court affirmed the Board's interpretation that the transition phrase "consists" did not limit the claims to only the recited numbered nucleotide sequences of SEQ ID NO:1 and that "the transition language comprising' allowed the claims to cover the entire involucrin gene plus other portions of the plasmid, as long as the gene contained the specific portions of SEQ ID NO:1 recited by the claim[s]" *Id.* at 1256, 73 USPQ2d at 1366.

In the instant case, the phrase "consists of" appears in the body of the claim rather than immediately following the preamble (for the rejected claims). Because the recombinant vectors can comprise other elements, the claims cover other portions of the alcohol oxidase regulatory sequences, as long as the recombinant vector contains the specific sequences recited by the claims. The references applied under 35 U.S.C. 102 above teach the specific portions required by the claims in the context of a recombinant vector, where the regulatory sequence is operably linked to a heterologous coding region.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over EP 0244598, cited in a prior action; see the entire reference) in view of Ohi et al (US Patent No. 5,683,893; see the entire reference), Maier et al (Nucleic Acids Research, Vol. 22, No. 16, pages 3423-3424, 1994; see the entire reference), and Buck et al (Biotechniques, Vol. 27, No. 3, pages 528-536, 1999; see the entire reference). This is a new rejection, necessitated by the addition of new claims 31-35 in the reply filed 6/18/2007.

Buckholz teaches an isolated DNA fragment from *Pichia* comprising a regulatory region containing instant SEQ ID NOS: 16, 17, 18, 19, 20 and 21. See claims 1-3 and plasmid pSAOH5 in Figure 2. Plasmid pSAOH5 is the same plasmid used in the instant specification to isolate the AOX1 promoter sequences, and thus it would necessarily have the same sequence as the instant sequence identifiers. Buckholz teaches a recombinant vector comprising the DNA fragment (see page 4). Further, Buckholz teaches the construction of nucleic acid molecules that contain fragments of the AOX1 promoter sequence (e.g., Tables IX, X, XI). Buckholz teaches it is within the skill of the art to determine the AOX1 promoter sequence (e.g., page 5, Sequence A and Sequence B).

Buckholz does not teach isolated polynucleotides consisting of SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 or SEQ ID NO: 21.

Ohi et al teach the use of a *Pichia* AOX1 promoter sequence as a hybridization probe for the identification of AOX2 promoter sequences within a genomic library (e.g., column 7, line 40 to column 8, line 54). A radioactively labeled AOX1 probe was used in the *in situ* filter hybridization assay to identify AOX2 clones (e.g., column 8).

Maier et al teach a method of making probes for *in situ* colony filter hybridization where the probes are labeled with biotin or digoxigenin, which obviates the need to use hazardous radioactivity (e.g., page 3423, left column, paragraph 1; paragraph bridging pages 3423-3424). Maier et al teach that long probes such as PCR products can be labeled with digoxigenin or biotin (e.g., paragraph bridging pages 3423-3424). Further, Maier et al teach that probes of any length labeled with biotin or digoxigenin have been successfully hybridized (e.g., page 3423, left column, paragraph 1).

Buck et al expressly provide evidence of the equivalence of primers. Specifically, Buck et al invited primer submissions from a number of labs (39) (e.g., page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck et al also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18-mer primers on the 300 base pair sequence (e.g., page 530, column 1). When Buck et al tested each of the primers selected by the methods of the different labs, Buck et al found that every single primer worked (e.g., page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (e.g., page 533, column 1). Buck et al expressly states, "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality" (e.g., 535, column 2). Therefore, Buck et al provide direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target

region. This clearly shows that every primer would have a predictable outcome and reasonable expectation of success.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Buckholz to limit the sequences of the AOX1 promoter to isolated nucleic acid molecules consisting of SEQ ID NO: 16, 17, 18, 19 or 21. Buckholz teaches plasmid pSAOH5, which contains the entire AOX1 promoter and each of the sequences defined by SEQ ID NO: 16, 17, 18, 19 or 21. One would have been motivated to make such a modification in order to use the sequences as probes in an *in situ* colony filter hybridization assay, as taught by Ohi et al and Maier et al, to identify additional genomic clones containing AOX2 or AOX1 sequence, without the need to use hazardous radioactivity. Buckholz teaches it is within the ordinary skill of the art to determine the sequence of the AOX1 promoter, and Buck et al teach it is within the ordinary skill of the art to design any primer to a known nucleic acid sequence. Thus, it would have been obvious to one having ordinary skill in the art to design primers to the AOX1 promoter for PCR, which would result in sequences consisting of SEQ ID NO: 16, 17, 18, 19 or 21. Further, Maier et al provide evidence that each of the probes obtained by PCR and consisting of SEQ ID NO: 16, 17, 18, 19 or 21 would successfully hybridize to complementary sequences in an *in situ* colony filter hybridization assay. Combining the teachings of Buckholz, Ohi et al, Maier et al, and Buck et al would achieve the predictable results of obtaining an isolated nucleic acid molecule consisting of SEQ ID NO: 16, 17, 18, 19 or 21.

Response to Arguments - 35 USC § 103

The rejection of claims 26-29 under 35 U.S.C. 103(a) as being unpatentable over Buckholz in view of Romanos et al is moot in view of Applicant's cancellation of the claims in the reply filed 6/18/2007.

Conclusion

Claims 23, 36-38, 40, 42, 44, 46, 48, 50, 52 and 54 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Dunston, Ph.D.
Examiner
Art Unit 1636

/JD/

CELINE QIAN, PH.D.
PRIMARY EXAMINER